The impact of ex vivo clinical grade activation protocols on human T-cell phenotype and function for the generation of genetically modified cells for adoptive cell transfer therapy.

Journal: J Immunother

Publication Year: 2010

Authors: Paul C Tumeh, Richard C Koya, Thinle Chodon, Nicholas A Graham, Thomas G Graeber, Begona Comin-Anduix, Antoni Ribas

PubMed link: 20842061

Funding Grants: Stem Cells for Immune System Regeneration to Fight Cancer

Public Summary:
Adoptive cell therapy involves the ex vivo genetic manipulation of lymphocytes that are infused back into patients. Optimized conditions for the ex vivo activation, genetic manipulation, and expansion of human lymphocytes for adoptive cell therapy may lead to clinical protocols that maximize their in vivo function. We analyzed the effects of 4 clinical grade activation and expansion protocols over 3 weeks on cell proliferative rate, immunophenotype, cell metabolism, and transduction efficiency of human peripheral blood mononuclear cells (PBMCs). Peak transduction efficiency using a lentiviral vector was early (days 2 to 4), at a time when cells showed a larger size, maximal uptake of metabolic substrates, and the highest level of proximal T-cell receptor signaling engagement. Anti-CD2/3/28 activation beads induced greater proliferation rate and skewed PBMCs early on to a CD4 phenotype when compared with the cells cultured in OKT3. Multicolor surface phenotyping demonstrated that changes in T-cell surface markers that define T-cell functional phenotypes were dependent on the time spent in culture as opposed to the particular activation protocol. In conclusion, ex vivo activation of human PBMCs for adoptive cell therapy demonstrate defined immunophenotypic and functional signatures over time, with cells early on showing larger sizes, higher transduction efficiency, maximal metabolic activity, and zeta-chain-associated protein-70 activation.

Scientific Abstract:
Optimized conditions for the ex vivo activation, genetic manipulation, and expansion of human lymphocytes for adoptive cell therapy may lead to protocols that maximize their in vivo function. We analyzed the effects of 4 clinical grade activation and expansion protocols over 3 weeks on cell proliferative rate, immunophenotype, cell metabolism, and transduction efficiency of human peripheral blood mononuclear cells (PBMCs). Peak lentiviral transduction efficiency was early (days 2 to 4), at a time when cells showed a larger size, maximal uptake of metabolic substrates, and the highest level of proximal T-cell receptor signaling engagement. Anti-CD2/3/28 activation beads induced greater proliferation rate and skewed PBMCs early on to a CD4 phenotype when compared with the cells cultured in OKT3. Multicolor surface phenotyping demonstrated that changes in T-cell surface markers that define T-cell functional phenotypes were dependent on the time spent in culture as opposed to the particular activation protocol. In conclusion, ex vivo activation of human PBMCs for adoptive cell therapy demonstrate defined immunophenotypic and functional signatures over time, with cells early on showing larger sizes, higher transduction efficiency, maximal metabolic activity, and zeta-chain-associated protein-70 activation.